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# Treatment of acute respiratory failure in the course of COVID-19. Practical hints from the expert panel of the Assembly of Intensive Care and Rehabilitation of the Polish Respiratory Society

## Abstract

In 2019, a pandemic began due to infection with a novel coronavirus, SARS-CoV-2. In many cases, this coronavirus leads to the development of the COVID-19 disease. Lung damage in the course of this disease often leads to acute hypoxic respiratory failure and may eventually lead to acute respiratory distress syndrome (ARDS). Respiratory failure as a result of COVID-19 can develop very quickly and a small percent of those infected will die because of it. There is currently no treatment for COVID-19, therefore the key therapeutic intervention centers around the symptomatic treatment of respiratory failure. The main therapeutic goal is to maintain gas exchange, mainly oxygenation, at an appropriate level and prevent the intensification of changes in the lung parenchyma. Depending on the severity of hypoxemia different techniques can be used to improve oxygenation. Medical staff dealing with COVID-19 patients should be familiar with both, methods used to treat respiratory failure and the epidemiological risks arising from their use. In some patients, conventional (passive) oxygen therapy alone is sufficient. In patients with worsening respiratory failure high flow nasal oxygen therapy (HFNOT) may be effective. The continuous positive airway pressure (CPAP) and non-invasive ventilation (NIV) methods can be used to a limited extent. With further disease progression, invasive ventilation must be used and in special situations, extracorporeal membrane oxygenation (ECMO) can also be administered.

The authors of this article set themselves the goal of presenting the most current knowledge about the epidemiology and pathophysiology of respiratory failure in COVID-19, as well as the methods of its treatment. Given the dynamics of the developing pandemic, this is not an easy task as new scientific data is presented almost every day. However, we believe the knowledge contained in this study will help doctors care for patients with COVID-19. The main target audience of this study is not so much pneumonologists or intensivists who have extensive experience in the application of the techniques discussed here, but rather doctors of other specializations who must master new skills in order to help patients during the time of a pandemic.

**Key words:** acute respiratory failure, ventilatory support, non-invasive mechanical ventilation, high flow nasal oxygen therapy, COVID-19

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## Introduction

The pandemic caused by the SARS-CoV-2 virus has, suddenly and unexpectedly, caused health services to be faced with previously unknown and difficult challenges. Since the main complication of this infection is severe viral pneumonia, pneumonologists and infectious disease specialists

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occupy a special place in the fight against this pandemic. At the turn of 2002–2003 a similar epidemic broke out, also due to the coronavirus, but only on a local scale (Southeast Asia). Some infected patients developed severe pneumonia, which was characterized by a rapid clinical course and a high mortality rate due to acute respiratory failure. For this reason, this disease was called SARS, an acronym made from the first letters of the English name: severe acute respiratory syndrome. During that outbreak, there were 8096 confirmed cases and 774 deaths, which signifies a high mortality rate of 9.5%. The epidemic at that time did not spread globally, and only single cases were reported in European countries [1]. In 2012 there was the second outbreak of epidemic caused by coronavirus, which took place in Middle East and Northern Africa regions. Due to location it was called Middle East Respiratory Syndrom (MERS). Till 2017 2040 cases and 712 deaths was noted [2, 3].

As in 2002 and 2012, the cause of the current pandemic is the coronavirus, hence the name SARS-CoV-2. The receptor for this virus in the human body is the angiotensin II converting enzyme, whose significant expression is present in, among others, the respiratory epithelial cells [4]. That explains why the virus has a special affinity for the lungs, among other organs. Since the world's first reported incident of infection with the SARS-CoV-2 virus, the number of infected people has grown exponentially and has now exceeded eight million, of which over 465,000 have died. Infected patients have been found in every country of the world [5]. The massive number of seriously ill patients suddenly requiring medical attention shocked and overwhelmed the health care systems of even the richest countries, with painful examples being Italy, Spain, and the USA. Compared to other Western European countries, the pandemic reached Poland with some delay giving authorities and health care workers time to take preventive measures and learn from the experiences of other countries that first faced this pandemic. In this study, the authors, members of the Intensive Care and Rehabilitation Assembly of the Polish Respiratory Society (PTChP), present knowledge about the clinical picture as well as the methods of treating respiratory failure in the course of COVID-19.

## Clinical picture of COVID-19

The main source of information about patients infected with SARS-CoV-2 comes from Chinese reports, with some recent input also coming from Italy and the USA. Guan *et al.* [6] retrospectively described 1099 hospitalized patients. Contrary to popular belief, which stated the severe course of the disease affects only elderly patients, the average age of this group was 47 years old and almost 60% were men. Based on medical records, 173 patients (19%) were admitted in a severe condition. The risk factors for severe disease were advanced age and comorbidities. In the group of patients with a severe course, almost all patients (97%) had pathological changes in images produced by a CT scan of the chest on admission. Meanwhile, in the group of patients classified as having a mild course of the disease, only 19% had these changes. According to laboratory tests, severe patients had leukopenia and lymphocytopenia. 38% of severe patients required invasive ventilation, 15% required non-invasive mechanical ventilation (NIV), and 8% died. Zhou *et al.* analyzed a group of 191 hospitalized patients. Of these patients, 54% had respiratory failure and 2/3 of them developed ARDS, which was fatal in most cases. Respiratory acidosis was a rare phenomenon and was found in only 9% of all patients [7]. In an analysis of 201 hospitalized patients by Wu *et al.* [8], 82% of patients required oxygen therapy, including almost half (49% of the entire group) requiring low-flow oxygen supplementation through a nasal cannula. NIV was used in 30% of patients and 2.5% (5 patients) required intubation and invasive ventilation, including one patient who also needed extracorporeal blood oxygenation (ECMO). 53 patients (26%) required admission to the Intensive Care Unit (ICU), and 44 (22%) died. Risk factors for death, as in previous studies, were older age, coexistence of chronic diseases, as well as neutrophilia and high levels of LDH and d-dimer on admission. According to the results of the analysis of 73,000 COVID-19 cases in China, 81% of patients had a mild disease, 14% had a severe disease, and 5% had a critical disease. Mortality in this analysis was 2.3% [8] however, data on mortality vary from country to country. The highest rate of mortality (> 10%) was found in such countries as Italy, UK, and Belgium. One of the lowest rates was in Germany (< 1%) [9]. The mortality rate is most likely influenced by various factors ranging from healthcare organizations (i.e. number of beds in the ICU) to reporting methods and death qualifications.

Here we will discuss a typical course of severe COVID-19 [7]. The most commonly presented symptoms on admission are increased body temperature and dry cough. The temperature

does not have to be high as it can be < 37.5°C. On admission, changes in the CT scan of the lungs may be present. After five to seven days, dyspnea appears, which increases in the following days or even hours and may be the reason for urgent intubation and invasive ventilation. Since the disease progression rate may vary, each patient should be monitored constantly with a special focus on percutaneous measurement of the hemoglobin oxygen saturation ($SpO_2$).

An analysis of 1591 patients admitted to the ICU in Italy has recently been published [10] with 82% being male. Therefore, the male sex could be considered a risk factor for the development of severe disease. The average age of this group was 63 years, with 2/3 of patients having at least one comorbidity, most often being hypertension. Interestingly, COPD was present in only 8% of patients over 70 years of age and was rarer in younger patients (3%). In contrast, co-existing COPD is associated with up to a five-fold greater risk of severe COVID-19 [11]. Doctors should be aware that severe respiratory failure and ARDS may also occur in young people without any co-existing diseases. In a group of 1300 patients described by Grasselli *et al.*, data on the treatment of respiratory failure methods were presented. Almost everyone (98%) required ventilatory support; 1,150 (88%) patients needed invasive ventilation and only 137 (11%) were treated with NIV. 89% of patients required an oxygen supply with $FiO_2$ greater than 50% [10]. Data from the USA indicates a lower percentage of necessary intubation (71% of those treated in the ICU), but for now these are analyses of small groups of patients [12]. In China, the percentage of patients treated in the ICU and invasively ventilated ranged from 30% to 47% [13, 14], while NIV treated patients ranged from 14% to 62%. The varied data regarding the number of patients requiring invasive and non-invasive ventilation are probably due to different criteria for admission to the ICU, different criteria for invasive ventilation, and differing availability of medical equipment.

## Pathophysiology of respiratory failure in COVID-19

As the SARS-CoV-2 pandemic continues, we are able to learn more about the pathophysiological aspects of COVID-19. The main complication of the severe course of this disease is viral pneumonia, which causes edema of the interstitium of the lungs, most often located in the sub-pleural areas. Therefore, CT scans of the chest reveal multifocal, diffuse, most often bilateral ground-glass opacities. Despite the relatively small amount of lung parenchyma involved, severe hypoxemia may occur during this phase of the disease. The cause is not entirely clear, but most likely is due to a disturbance in the regulation of pulmonary vascular tone (vasoplegia), which does not constrict despite alveolar hypoxia. This causes a significant inadequacy in ventilation to perfusion ratio (V/Q mismatch). Since lung compliance is likely to be normal or only slightly reduced with such small lesions, the patient usually has no difficulty increasing ventilation to improve $PaO_2$, often leading to hypocapnia. Some Italian researchers describe this clinical picture (relatively small changes in chest imaging, normal lung compliance, and significant hypoxemia) as the disease's "L" phenotype. This name comes from the first letter of the English terms for four characteristics: 1. **L**ow elastance (high compliance, normal or nearly normal in this case), 2. **L**ow V/Q ratio (low ventilation to perfusion ratio), 3. **L**ow lung weight, and 4. **L**ow lung recruitability (weak effect of alveolar recruitment with positive airway pressure). The optimal form of treatment at this stage is passive oxygen therapy. At this stage, the disease may either go into the regression phase and towards recovery or into the progression of lung lesions towards ARDS. If the latter scenario takes place, the lung changes evolve into massive parenchymal infiltrates covering large areas of the lung, a typical image of ARDS. This phenotype was named after the letter "H" from the first letter of English words describing the characteristic pathophysiological features: 1. **H**igh elastance (low compliance), 2. **H**igh right-to-left shunt, 3. **H**igh lung weight, and 4. **H**igh lung recruitability (good response to the use of positive airway pressure in the form of alveolar recruitment and improved gas exchange). For phenotype H, the main mechanism of hypoxemia is right-to-left intrapulmonary shunt. Areas of the lung parenchyma involved in the inflammatory process are not ventilated while the perfusion is still ongoing, therefore, there is no gas exchange. Blood that perfuses these areas returns to the systemic circulation as still poorly oxygenated venous blood. The greater the amount of blood that flows through the affected (unventilated) lung parenchyma, the greater the hypoxemia. Figure 1 presents the mechanism of hypoxemia by way of right-to-left intrapulmonary shunt. The use of positive airway pressure for ventilatory support (active oxygen therapy) is the treatment of choice in the H phenotype [15]. It is important to take into consideration

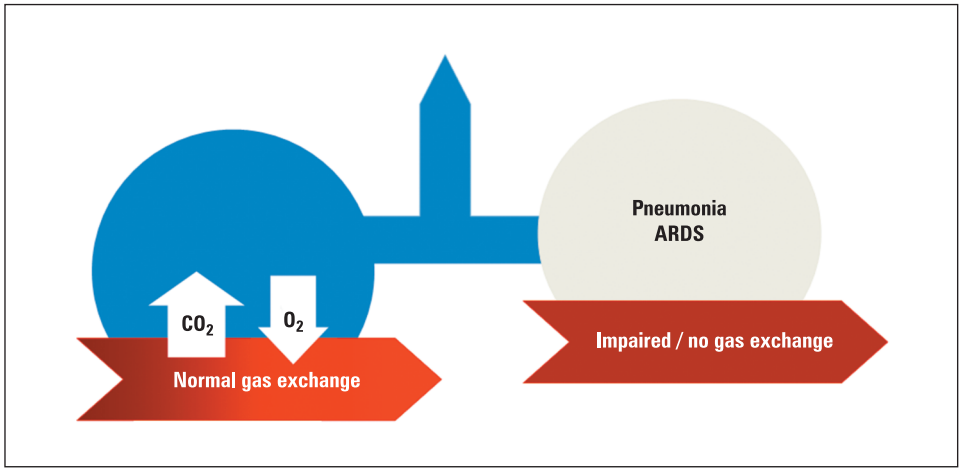


**Figure 1.** Schematic mechanism of hypoxemia (intrapulmonary shunt). On the left-hand side, a normal perfusion ventilation ratio can be seen, on the right-hand side, diseased lung area can be seen. In this area there is no ventilation, therefore no blood oxygenation may take place. In cases where the addition of non-oxygenated blood is large, the use of passive oxygen therapy will be probably ineffective, because the administered oxygen does not reduce intrapulmonary shunt, but only improves the oxygenation of blood passing through healthy pulmonary parenchyma

that prolonged strenuous respiratory effort may exacerbate (worsen) respiratory failure and cause a transition from "L" to "H" phenotype [15]. This phenomenon is called patient self-inflicted lung injury (P-SILI) and plays an important role in the pathophysiology of ARDS (caused not only by COVID-19). For this reason, ventilatory support (mechanical ventilation/CPAP/NIV) should not be delayed in patients with high respiratory effort. The described changes in lung parenchyma are presented in Figures 2 and 3.

In addition, hypercoagulability, which increases the risk of thrombosis, is also a characteristic of the severe course of COVID-19. Therefore, another mechanism by which hypoxemia can be caused and/or exacerbated is via pulmonary embolism. One report from a French center stated pulmonary embolism was found in 20% of 107 patients hospitalized in the ICU which, according to the authors, more than doubled the incidence of this complication among the general population of patients treated in the ICU [16].

## Treatment of hypoxemia

Since there is no specific treatment for COVID-19, maintaining respiratory function by ensuring proper gas exchange and, above all, adequate oxygenation of blood is the most important therapeutic goal. Below, we will discuss methods of treating hypoxic respiratory failure starting with the simplest techniques allowing the use of a lower fraction of oxygen in inhalation gases ($FiO_2$) all the way up to advanced techniques that allow the supply of high fraction of oxygen, even up to 100% under positive pressure. This does not mean that every patient should be started with a nasal cannula and all oxygen therapy techniques should be used in succession. On the contrary, depending on the patient's initial state, severity of hypoxemia, respiratory effort, available equipment, possibility of patient isolation, and the possibility of implementing invasive ventilation, one should start with a treatment method that will ensure satisfactory oxygenation of blood while also taking the safety of the staff into account. Transcutaneous pulse oximetry should be used in the assessment of blood oxygenation due to its availability, ease of application, and possibility of continuous measurement of this vital parameter. Assessment of the partial pressure of oxygen ($PaO_2$) should only be used if there are doubts about the reliability of the $SpO_2$ measurement or if there is suspected hypercapnia. False $SpO_2$ measurements may occur in the following clinical situations: improperly fitted sensor (not fully covering the distal phalanx), peripheral hypoperfusion, hypotension, arrhythmia, damaged distal phalanx, or if a patient has dark nail polish covering their fingernail. There is no consensus among scientific bodies regarding the optimal $SpO_2$ value that should be achieved under the influence of treatment. The British Thoracic Society has recommended the $SpO_2$ target to be between 94–98% since 2008 [17]. Currently, the WHO also recommends maintaining $SpO_2 > 94\%$ in guidelines for the treatment of respiratory

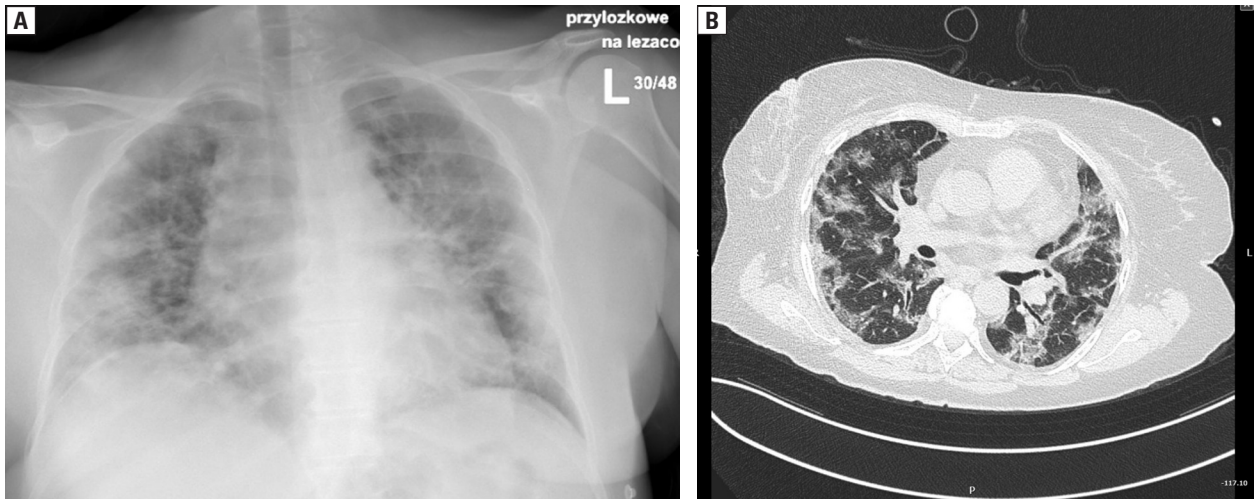


**Figure 2.** Picture of lung parenchyma involvement on the 4th day of treatment of 56-year-old woman infected with SARS-CoV-2. In chest anterior-posterior radiograph (**A**) and high resolution computer tomography (**B**) areas of grand glass opacities, mainly with sub-pleural predominance. Respiratory insufficiency. Treatment with Venturi mask — $FiO_2$ 0.4 to be able to reach $SpO_2$ 94%

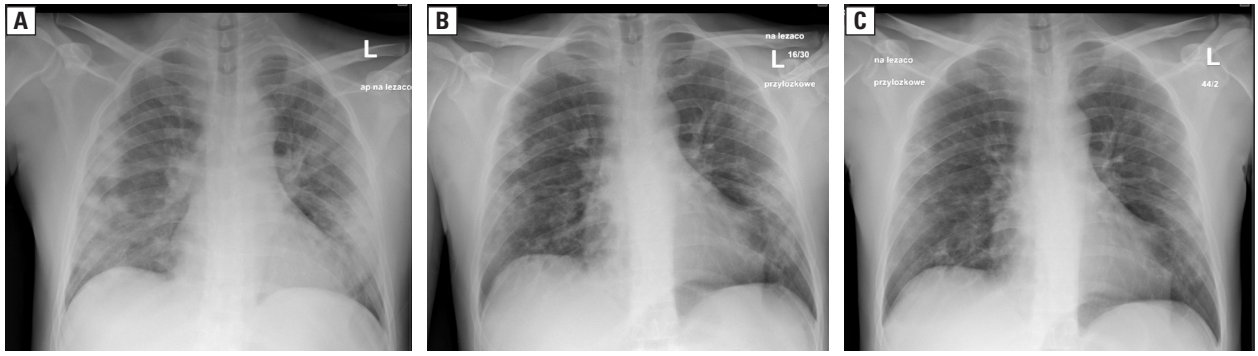


**Figure 3.** The course of COVID-19 in 37-year-old male in chest radiograph examinations. **A**. The admission day: disseminated parenchymal opacities in both lungs. **B**. 5th day of hospitalization. **C.** 16th day of hospitalization. Visible gradual regression of the lesions. The patient with respiratory failure — required the use of oxygen with nasal cannula (flow 5 L/min). On day 16th the patient without hypoxemia

failure in COVID-19 [18]. On the other hand, a panel of international experts in the field of intensive therapy draws attention to the harmful effects of hyperoxia (increased risk of death) and in a document issued in 2018, recommended maintaining $SpO_2$ at 90–94% [19]. The European Intensive Care Society also recommends that $SpO_2$ should not exceed 96% during the treatment of COVID-19 respiratory failure [20]. Regardless of which guidelines we adopt, treatment should never allow for $SpO_2$ to fall below 90%. It seems that the target $SpO_2$ should be between 92% and 96%. In the case of a patient with chronic hypercapnic respiratory failure, the recommendations are unambiguous. $SpO_2$ should be maintained within 88–92% so as not to weaken the hypoxic respiratory drive and to not increase hypercapnia.

## Conventional (passive) oxygen therapy

Passive oxygen therapy refers to spontaneous breathing air with an increased oxygen content, which means a $FiO_2$ within a range of 0.22 to 1.0 (22% to 100%). This treatment can be performed with the use of devices described below:

### A. Nasal cannula

The nasal cannula is the simplest device for oxygen administration (Figure 4). The oxygen fraction is titrated by changing oxygen flow through the cannula. Pure (100%) oxygen, which comes out of the cannula, is blended in the patient's nostrils with the inhaled air to form a mixture of air and oxygen. This method does not allow for the administration of an inspiratory gas with a precise $FiO_2$ value since it depends on

**Figure 4**. Oxygen therapy with nasal cannula. Flow range should be titrated between 0.5 L/min and 6 L/min. This interface provides $FiO_2$ up to 0.4. Breathing with open mouth does not reduce $FiO_2$ and is not a contraindication to use of nasal cannula

**Figure 5**. Oxygen therapy with the use of a simple oxygen mask

the patient's minute ventilation. The generally accepted $FiO_2$ estimation method (an increase of 4% with an increase in oxygen flow by 1 L/min) can be unreliable in patients with high respiratory drive and high minute ventilation. It is believed that the flow should not exceed 6 L/min as a further increase in oxygen supply no longer significantly increases $FiO_2$. For nasal cannula oxygen therapy, COVID-19 patients may be fitted with surgical masks to minimize the risk of dispersion of aerosol.

## B. Simple oxygen mask

A simple oxygen mask is a frequently used interface in general wards (Figure 5). Its advantage lies in the possibility to provide higher $FiO_2$ [within 0.4–0.6 (40–60%)] compared to oxygen therapy via a nasal cannula. However, its disadvantage is the lack of strict control of $FiO_2$ administered and the risk of $CO_2$ re-inhalation. To avoid this risk, oxygen flow should not be less than 5 L/min. The maximum flow is considered to be 10 L/min.

## C. Venturi mask

If the nasal cannula or simple oxygen mask cannot provide adequate blood oxygenation, a Venturi mask can be used (Figure 6). The advantage of this mask is the ability to administer a mixture of air and oxygen with a constant and precisely selected oxygen fraction in the range of 24% to 60%. The $FiO_2$ value is determined by selecting the appropriate sized port (Figure 7) and setting the appropriate oxygen flow assigned to the Venturi port. It should be remembered that the given oxygen flow rate is the minimum value that should be set. Therefore, it is not an error to set a higher flow rate when high minute ventilation is suspected. However, as the flow through the mask increases, the dispersion of exhaled gas in the room is also greater [21].

## D. Non-rebreather mask

If oxygen therapy with a 60% Venturi mask is insufficient, a non-rebreather mask should be used (Figure 8). The principle mechanism of action of this mask is, with each breath, to inhale pure oxygen from the reservoir attached to the mask. The one-way valve system prevents the exhaled and

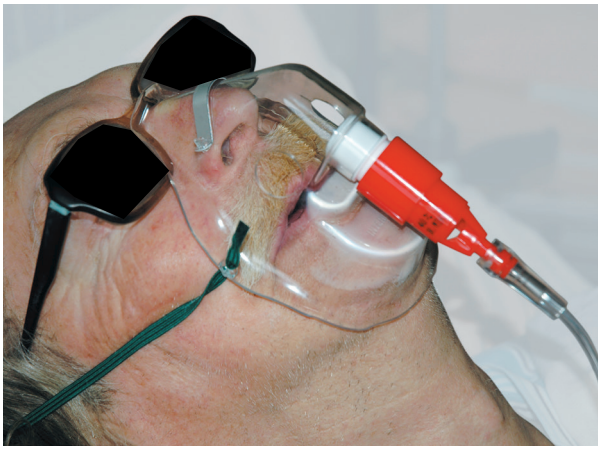

**Figure 6**. Oxygen therapy with the use of Venturi mask. The red item is a Venturi sized port, where air and oxygen is blended to provide exact $FiO_2$ between 24% and 60%


**Figure 7**. Venturi sized ports. In order to deliver certain $FiO_2$ the adequate port has to be implemented between mask and cannula, and indicated oxygen flow rate has to be set up

inhaled air from mixing. In order for this treatment to be effective, the mask must be tightly fitted to the face so the patient does not breathe in air from the room and the oxygen reservoir must be filled promptly so the entire inspiratory volume comes from it. With correct use, it is possible to achieve a $FiO_2$ of 0.8–0.95. The use of a non-rebreather mask is the safest method to avoid medical personnel being infected because the expiratory aerosol is dispersed the smallest distance from the patient's mouth, approximately 10 cm [22].

## High-flow nasal oxygen therapy

### A. Principle of operation

High-flow nasal oxygen therapy (HFNOT) refers to administering high flow air (10–60 L/min.) enriched with oxygen at a concentration ranging from 22% to 100% through dedicated nasal prongs (Figure 9). In addition, the gas mixture is saturated with moisture and heated to a temperature of 31–37°C, which closely mirrors the natural conditions in the nasal cavity. Thanks to this, the patient tolerates high airflow very well. This would not be possible with dry, cool gas [23]. HFNOT is an intermediate method between passive and active oxygen therapy. HFNOT has several beneficial effects on pathophysiology of respiratory failure. Firstly, high gas flow generates positive airway pressure (an increase in flow rate by 10 L/min results in an increase in airway pressure from 0.5–1.0 $cmH_2O$), which increases functional residual capacity (FRC) and causes alveolar recruitments, enhancing gas exchange. Secondly, reduction of expiratory gases retention in the dead space. Thirdly, in patients with obstruction, high inspiratory flow and positive airway pressure reduce the work of breathing [24]. Figure 10 shows the HFNOT device and explains its principle of operation.

**Figure 8**. Non-rebreather mask. Fully expanded reservoir bag, which contains pure oxygen, means effective oxygen flow in. This interface provides $FiO_2$ at the level of 80–95%

### B. Scientific evidence

To date, no randomized clinical trials have been conducted to assess the effectiveness of HFNOT in the treatment of COVID-19 respiratory failure, but this method has been commonly used in China. A retrospective analysis of 610 patients commonly treated with HFNOT found a lower necessity for intubation and lower mortality rate compared to data from neighboring regions of China where HFNOT was not used [25]. Earlier observations during the influenza epidemic in 2009 also pointed to the beneficial effects of HFNOT, although they were made on a small group of patients [26].

**Figure 9.** The interface for high-flow nasal cannula therapy

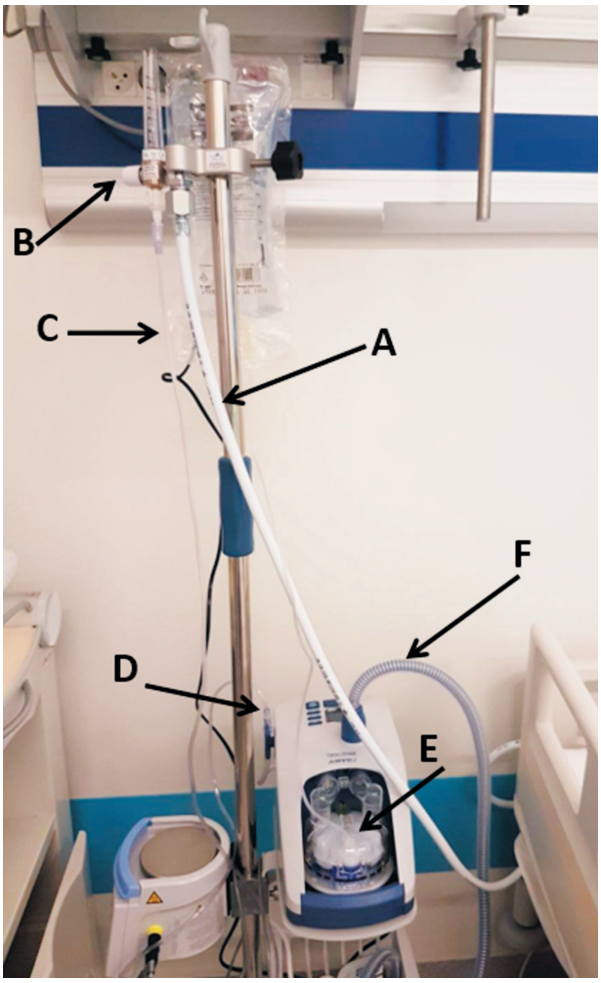


**Figure 10**. High-flow nasal cannula (HFNOT) device (AirVo2, Fisher&Paykel Healthcare, Auckland, New Zealand). **A.** High pressure oxygen circuit; **B.** High flowmeter (up 60 L/min); **C.** Oxygen cannula; **D.** Oxygen inlet with integreted blender and analyzer; **E.** Reservoir with distillated water supplied continuously (note the liquid bag on the top of rack), which serves as gas heater and humidifier; **F.** Inspiratory circuit leads the gas to nostrils

The randomized study assessing the effectiveness of HFNOT in the treatment of hypoxic respiratory failure showed a reduction in mortality in patients treated with HFNOT ($PaO_2/FiO_2$ < 300 mm Hg) compared to groups treated with conventional oxygen therapy (non-rebreather mask) or NIV [27]. This study also found a reduction in the risk of intubation in a subset of patients with an oxygenation index ($PaO_2/FiO_2$) < 200 mm Hg. These observations became the basis for recommending HFNOT in the treatment of acute hypoxemia in COVID-19 in the first place, prior to the use of NIV. It is worth noting, this study did not include patients with chronic respiratory diseases and cardiogenic pulmonary edema (clinical situations in which NIV has proven clinical efficacy). A meta-analysis of several randomized trials also confirmed that HFNOT reduces the risk of intubation [28] and the number of ICU admissions compared to conventional oxygen therapy [29]. These observations indicate that HFNOT can be used to treat hypoxic respiratory failure in COVID-19, especially where access to intensive care beds and ventilators is limited. WHO [18], the European Intensive Care Society [20], and numerous national scientific societies recommend this method.

## C. Parameter titration

The optimal initial setting of gas flow (maximum or minimum) remains a matter of debate. Lower flow rates (35–40 L/min) are better tolerated [30], while a larger flow rate (40–60 L/min) achieves clinical benefits in a shorter time. These benefits include relieving shortness of breath, improving oxygenation, and preventing inspiratory muscle fatigue [27]. In the case of a more severe clinical condition, you can start with a higher flow rate (e.g. 60 L/min) at the beginning to achieve rapid improvement and then titrate according to therapeutic goals and patient comfort [31]. Initial settings should be regularly adjusted to the patient's current respiratory rate (so it reaches < 25–30 breaths/min), $SpO_2$ (> 90%), and treatment tolerance. If therapeutic goals are achieved, the flow rate should be reduced by 5–10 L/min every one to two hours. However, if the goals are not achieved, it is suggested to gradually increase the airflow rate by 5–10 L/min up to 60 L/min and then increase $FiO_2$. If the patient's clinical condition and $SpO_2$ improve, we do the opposite by first lowering the $FiO_2$ and then gradually reducing the amount of airflow by 5–10 L/min at a pace that is dependent on the patient's clinical condition. If

the patient remains stable for one to two hours at an $FiO_2 \leq 0.4$ and airflow rate < 15 L/min, HFNOT can be discontinued and passive oxygen therapy can be started.

If the patient needs to be intubated, HFNOT can initially be used to improve oxygenation during laryngoscopy. In this case, the maximum flows and $FiO_2$ (flow 60 L/min, $FiO_2$ 1.0) should be used [32, 33]. HFNOT has been shown to minimize adverse events such as desaturation severity, arrhythmias, and cardiac arrest during intubation [33].

Unfortunately, in the age of the SARS-CoV-2 pandemic, the use of HFNOT may be associated with an increased risk of infection of medical personnel because during this process the exhaled air is dispersed in the form of aerosol droplets. However, research has shown that the distance of dispersion is not great. With an airflow of 60 L/min, the distance is less than 20 cm [34]. During the 2003 epidemic with SARS-CoV-1, reports do not indicate that the use of HFNOT was a risk factor for personnel infection [35]. In order to minimize this risk, the latest German guidelines recommend putting surgical masks on the patient's face [36].

### Active oxygen therapy

If the use of passive oxygen therapy or HFNOT is ineffective and we do not achieve a $SpO_2 \geq 90$–92% or if the patient's respiratory effort is not reduced, active oxygen therapy should be initiated. It refers to the inhalation of inspiratory gases at a positive pressure (higher than atmospheric pressure). Positive airway pressure may be delivered invasively by intubating the patient and starting mechanical ventilation or may be provided in a non-invasive manner through various types of interfaces (masks) applied to the patient's face. The purpose of positive airway pressure is, among others, to recruit alveoli and increase the gas exchange area, as well as to prevent the occurrence of atelectasis in the lung parenchyma. The therapeutic effect is not always predictable and depends on the amount of pressure used and the nature and distribution of lung lesions. Positive airway pressure operation is demonstrated in Figure 11.

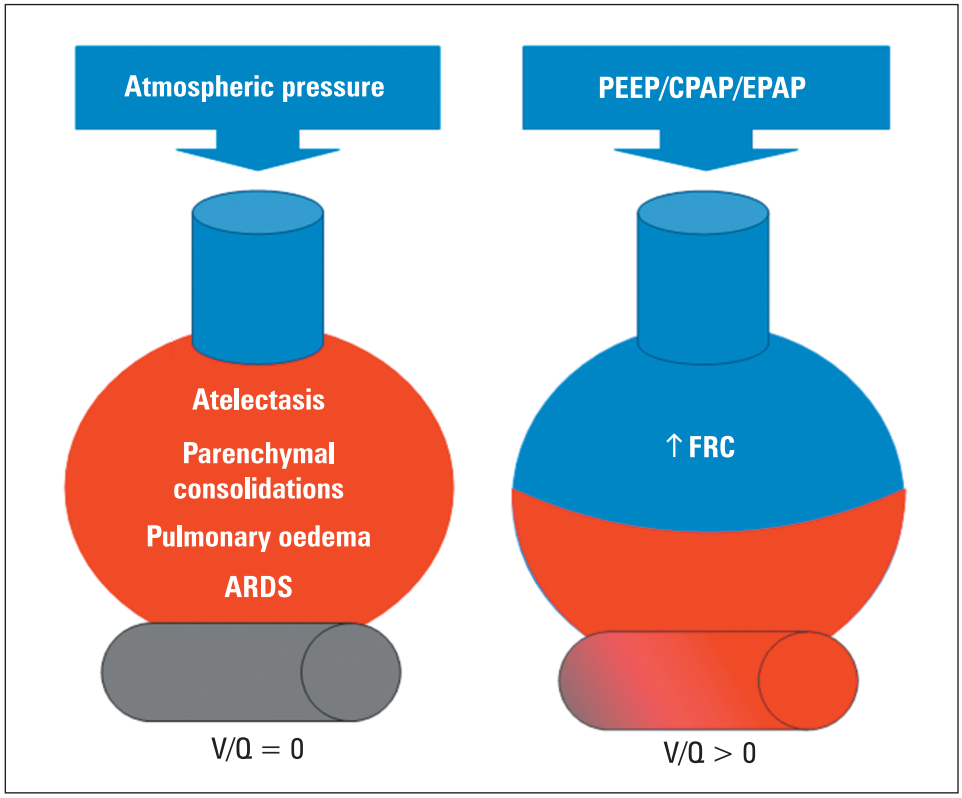


**Figure 11**. Schematic effect of the mechanism in which the positive airway pressure improves arterial blood oxygenation. The diagram on the left-hand side illustrates the part of the pulmonary parenchyma that is involved in the disease (**red color**), due to the lack of ventilation in these areas, the ratio of ventilation (**V**) to perfusion (**Q**) is zero. This means that there is no gas exchange between the blood and the alveoli (intrapulmonary shunt). The diagram on the right-hand side shows the use of positive airway pressure, which increases the gas exchange surface (so-called alveolar recruitment) (**blue**) and improves the ventilation to perfusion ratio, thanks to which gas exchange occurs in some of the blood

In most publications on the treatment of hypoxic respiratory failure, the authors use the common name for continuous positive airway pressure (CPAP) and describe it as non-invasive mechanical ventilation (NIV). This is justified by the fact that these patients require the application of positive airway pressure and not augmenting ventilation (i.e. bilevel positive airway pressure, BiPAP). However, from a physiological point of view, due to the fact that CPAP is not a method of ventilation in the literal sense, we will discuss both modes of non-invasive active oxygen therapy separately. CPAP will be understood as a mode of constant pressure and NIV understood as a mode of bi-level airway pressure (BiPAP).

## A. Continuous positive airway pressure (CPAP)

The CPAP mode delivers gas into the respiratory system during inspiration and exhalation at a constant pressure higher than the atmospheric pressure. It is widely used in medicine, primarily in the treatment of obstructive sleep apnea [37]. PEEP (positive end-expiratory pressure) refers to positive airway pressure at the end of exhalation in intubated patients and is used in intensive care in the treatment of ARDS [38]. The possibility of using CPAP in the treatment of respiratory failure was already reported during the SARS-CoV-1 epidemic [39]. That being said, we do not have clinical trial results that allow us to provide clear guidelines on when and how to use CPAP in the treatment of patients infected with SARS-CoV-2. With this in mind, current clinical experience from doctors in Southern and Western Europe argue that this method can be effective in a certain group of patients. Constructed strategies for the treatment of COVID-19 also suggest taking this method into account [40], especially in patients without hypoventilation, which is typical for patients with COVID-19.

The advantages of CPAP therapy include high availability, low cost, no need to have high medical competence when using it, no patient-device asynchrony (possible when using ventilation), high safety of treatment, and the possibility of using the patient's own CPAP device (if the patient uses this method in treatment of sleep apnea). It should also be noted that the use of CPAP in improving oxygenation might be even more effective than when using NIV, as the mean respiratory pressure value during ventilation with bilevel positive airway pressure (BiPAP) is usually lower than the CPAP values, which are significantly higher. Moreover, a lack of increase in inspiratory volume through the use of CPAP, as opposed to NIV, may have additional significance in the treatment of this group of patients as it is part of the strategy of protecting lungs from overdistension (volutrauma and barotrauma) [41].

### Indications for CPAP (non-invasive CPAP therapy)

We do not have clear guidelines based on strong scientific evidence determining the criteria for CPAP treatment. This therapy should be considered when passive oxygen therapy or HFNOT is ineffective and should be undertaken before invasive ventilation is started if the patient's status allows for this. A consultant intensivist makes this decision. The main purpose of using CPAP is to protect the patient against the need for intubation. The guidelines proposed by various scientific societies are based mainly on reports from regions with the most experience in the treatment of the COVID-19 disease. Decisions to initiate or discontinue this form of therapy should be taken individually and must take into account the following aspects:

1. Patient's condition (risk of intubation);
2. Planned escalation of therapy (whether the patient would be qualified for invasive ventilation if his condition worsens or not);
3. Availability of medical equipment (i.e. CPAP devices, masks);
4. Experience of medical staff in its application;
5. Options for protecting medical staff against infection.

The British Thoracic Society (BTS) suggests starting CPAP therapy if the significant respiratory effort and respiratory rate ≥ 20 min persists and when, despite passive oxygen therapy with $FiO_2 \geq 0.4$, $SpO_2$ is below 94% [42]. In addition, the coexistence of obstructive sleep breathing disorders (it is worth considering unrecognized obstructive sleep apnea, especially in obese patients) may be an additional indication for early use of CPAP in patients hospitalized due to COVID-19.

### How to use CPAP therapy in the treatment of COVID-19?

**Interfaces.** When choosing the type of interface, take into consideration both the possibility of conducting effective therapy as well as the safety of medical personnel. The characteristics of individual types of interfaces are presented in Table 1. Given this information and considering the quick and vast spread of the disease, as well as the danger that it poses, it seems the most

**Table 1. Comparison of interfaces used in conducting non-invasive active oxygen therapy (CPAP or bi-level PAP)**

| | Helmet | Nasal mask | Oral-nasal mask | Full face mask |
|---|---|---|---|---|
| |  |  |  |  |
| Unintentional leakage | Generally absent when the collar is inflated around the neck | Frequently excessive due to breathing through the open mouth | It is common but manageable in most patients | Usually relatively small and manageable in most patients |
| Pressure ulcers on patients face with prolonged use | Are not present | They are very common on the nose bridge | They occur in almost all patients on nasal bridge | Very rarely |
| The possibility of using high pressures | Unlimited | Usually poor tolerance and very large leaks | Often poor tolerance and large leaks | Often poor tolerance due to very large leaks |
| Ease to use by staff | Dedicated to handle by training and experienced staff | Relatively simple | Relatively simple | Relatively simple |
| Communication with the patient's environment | Possible, though difficult | Normal, the patient can communicate | Limited | Limited |
| Fluid oral intake | Possible through a special channel dedicated to carry the fluid probe | Convenient | Requires mask removal | Requires mask removal |

**Figure 12**. Non-invasive ventilation with the use of helmet and double limb respiratory circuit. On the left-hand side inspiratory arm of the circuit comes to the helmet (**black arrow**), on the right-hand side expiratory arm with antiviral filter (**empty arrow**)

optimal type of interface is a helmet. Despite the lack of hard scientific evidence, it is believed that it has the smallest risk of infection, due to the fact that the patient breathes in a closed space under the helmet and the air escaping from the helmet passes through a filter (Figure 12) [43]. In addition, the helmet is the best fitting interface available thanks to the flexible, cuffed collar

around the neck, which further reduces the risk of spraying aerosol droplets containing the virus. The helmet perfectly controls leaks in spite of a high pressure under it, which is extremely important in terms of effective treatment. Another advantage of the helmet is the possibility of long-term treatment. Since the helmet is not leaning on any part of the face, there are no pressure sores on the skin. However, an important side effect is the noise generated by the air flowing inside the helmet. It is recommended for the patient to wear earplugs when using this interface. In addition, a complication that may occur is swelling of the upper limbs, due to the pressure created by the belts supporting the helmet, which pass under the armpits. The solution to this problem is to attach straps to the harness on the patient's hips.

The second best option is to use a full-face or oral-nasal mask. Nasal masks are not applicable in the treatment of patients with severe shortness of breath. These patients breathe through their open mouths, which causes large leaks and an inability to maintain therapeutic pressure, thus exposing staff to infection. When using a mask with ventilator, the respiratory circuit should be composed in such a way that the patient exhales through the antiviral filter. Therefore, masks with a leak port located in the mask itself should not be used and we instead recommend using non-vented masks (without an exhalation port). There are three variants of respiratory circuits with non-vented masks:

1. A double-limb (Figure 13);
2. A single-limb with an exhalation valve (Figure 14);
3. A single-limb with a leakage port (whisper swivel type) located in the distal part of the circuit before the filter (Figure 15).

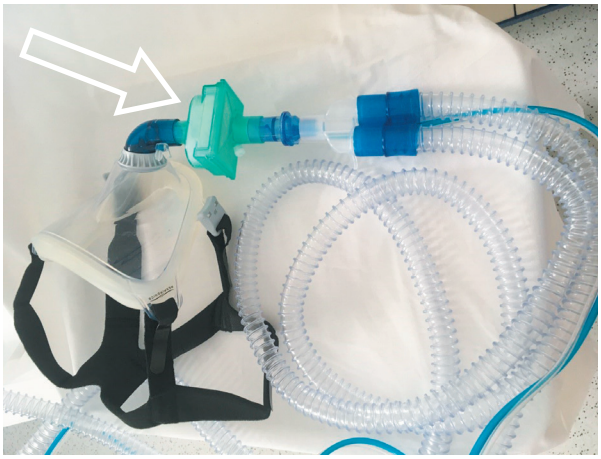

**Figure 13**. Double limb respiratory circuit for non-invasive ventilation or CPAP consist of inspiratory and expiratory limb. Note the non-vented mask and the antiviral filter (**empty arrow**) between the mask and the circuit

## CPAP devices

CPAP therapy may be provided be several various types of devices:

**Ventilator.** The optimal device for the use of CPAP in a patient with hypoxic respiratory failure is a ventilator, which allows for the titration of $FiO_2$ up to 100%. It is particularly advantageous to use a ventilator when applying positive pressure with an interface that has a large dead space (especially a helmet) because a large airflow is required, which simpler devices may not be able to generate.

**CPAP machine.** The most commonly used positive airway pressure generator is a CPAP device dedicated for home use. The problem with these devices lies in generating a gas mixture with $FiO_2$ greater than 0.4. If a high $FiO_2$ is needed, the oxygen supply to the respiratory circuit should be increased. To this end, pressure regulators with a flow greater than 15 L/min should be available. A device that generates a constant pressure of no less than 20 $cmH_2O$ is needed to use the helmet, so most home CPAP devices cannot be used with this interface.

**CPAP valve mask.** The pressure generator can be the flow of blended oxygen and air itself. A device called the Venturi Flow Generator/Driver, guarantees a sufficiently high flow (at least 40 L/min) in order to achieve the correct airway pressure level. The level of $FiO_2$ is regulated by a Venturi port and properly selected oxygen and airflow. Whereas, the CPAP level is generated by the exhalation valve (Figure 16).

The **Boussignac CPAP valve system** (Vygon, Ecouen, France), used the Bernoulli principle with a virtual valve effect [44], is the only commercially available device that does not incorporate an air-entrainment Venturi system. It is composed of a CPAP mask connected to a cylindrical plastic tube (Figure 17). Gas from an oxygen source flows through the four parallel micro-channels within the tube independently, creating turbulent gas flow and positive pressure within the hollow cylinder. The performance of the Boussignac CPAP system depends only on the delivered oxygen flow [45]. $FiO_2$ and positive pressure cannot be set by the operator because both are a result of the oxygen flow setting required to power the device and the amount of air the patient inhales above that delivered by the device.

**CPAP valve helmet.** Bearing in mind a high degree of security of helmet in COVID-19 therapy

**Figure 14**. Non-invasive ventilation with the use of non-vented full face mask and single limb respiratory circuit with expiratory valve. The expiratory valve (**black arrow**) opens only during expiration. Note the antiviral filter (**empty arrow**) between the mask and the expiratory valve

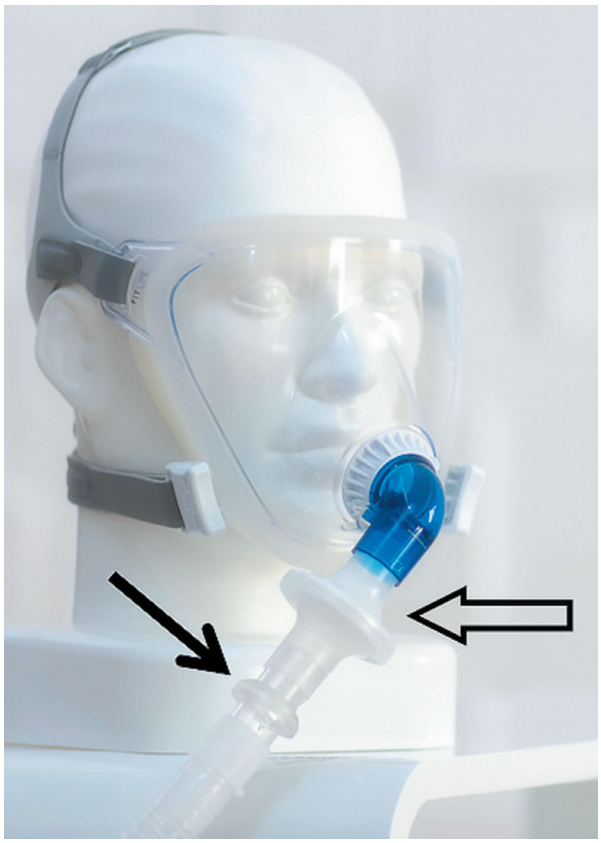

**Figure 15.** Non-invasive ventilation with the use of non-vented full face mask and single limb respiratory circuit with leak port. Note the leak port (**black arrow**) and antiviral filter (**empty arrow**) between the mask and the leak port

it is practical to consider to use continuous-flow CPAP generator with helmet with exhalatory valve. These are Venturi-effect flow generators, capable of delivering high flows up to 180 L/min and to adjust $FiO_2$ from 30% to 100%. An easy to use device even outside intensive care (ex. pneumology, internal medicine). For a proper CPAP therapy with the helmet, flows of air/oxygen of at least 40–50 L/min are needed. It can be used with all models of both helmets and masks for CPAP therapy. Continuous-flow CPAP generator with helmet with exhalatory valve is widely used in Italy.

## CPAP technical aspects

**Pressure titration.** The CPAP level determines the effectiveness of improving blood oxygenation. It is recommended to start using CPAP with pressures of 10–12 $cmH_2O$ and gradually increasing them to 20 $cmH_2O$ depending on how the patient tolerates treatment, leaks, and $SpO_2$. In an Italian study evaluating the treatment of 1,300 patients in the ICU, the average CPAP level was 14 $cmH_2O$, while the maximum was 22 $cmH_2O$ [10].

**Humidification.** Humidification of inhaled gases is not recommended because of the increased risk of aerosol spread [46].

**Treatment time.** The efficacy of CPAP therapy should be strictly monitored so there is no delay in escalating therapy to invasive ventilation if needed. The principles of patient monitoring should be based primarily on the analysis of the oxygenation index ($PaO_2/FiO_2$ or $SpO_2/FiO_2$) and evaluation of clinical parameters (i.e. respiratory rate, degree of shortness of breath, and level of consciousness). The assessment of these parameters should be carried out in the initial period of therapy (1–2 hours) constantly. If continuous monitoring of the patient is not possible, satisfactory efficacy and tolerance must be proven 30 minutes after commencement of CPAP therapy, during which time it should be used constantly to achieve clinical improvement.

Conducting CPAP treatment in prone position may have additional benefits in terms of

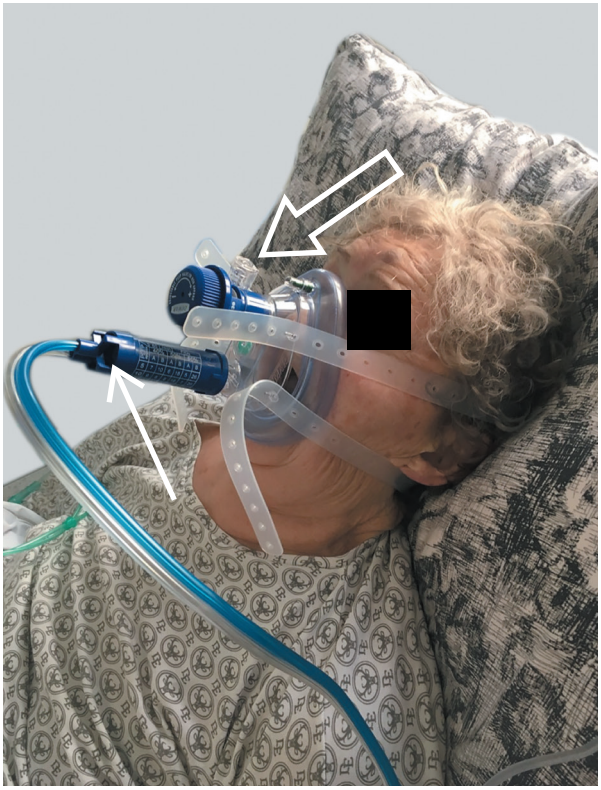

**Figure 16.** CPAP therapy with the use of Venturi Flow Generator (Easy Flow Venturi). Air and oxygen are delivered via separate cannulas to Venturi adjustable port (**white arrow**). The valve in the mask (**empty arrow**) generates positive pressure under the mask which can be titrated

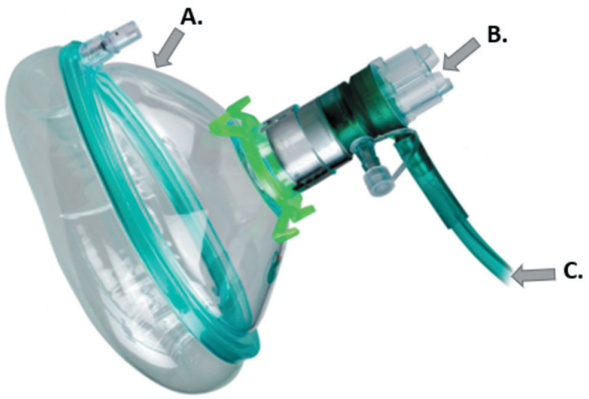


**Figure 17.** Boussignac CPAP system. The three components of the system includes: **A.** face mask; **B.** the Boussignac CPAP valve; **C.** oxygen tubing [68]

improved oxygenation. The authors found only one prospective study assessing the effectiveness of such therapy in a small group of 20 patients with moderate or severe ARDS in the course of viral pneumonia. Therapy in the prone position was carried out for two hours per day [47]. The results of this innovative study do not provide definitive conclusions about the effectiveness of this positioning, however, there are more and more studies on prone positioning in nonitubated patients with COVID-19 , especially from France [48] and Italy [49], stating that $pO_2$ is higher in the prone position rather than supine.

## B. Non-invasive ventilation (NIV) Treatment of de-novo acute respiratory failure

Non-invasive mechanical ventilation (NIV) is not the treatment of choice for acute (hypoxemic) respiratory failure (ARF, so called de-novo ARF) that occurs in most patients with COVID-19. De-novo ARF is defined as acute respiratory failure in a patient without chronic respiratory diseases characterized by severe hypoxemia (oxygenation index: $PaO_2/FiO_2 \leq 200–300$ mm Hg).

The most common causes of ARF are pneumonia or ARDS. There are a number of exceptional situations in which the use of NIV in ARF has been demonstrated to have a beneficial effect [50]:

1. ARF in an immunocompromised patient;
2. ARF as a post-operative complication;
3. ARF as a consequence of cardiogenic pulmonary edema;
4. ARF due to chest trauma.

The purpose of NIV in ARF is to improve blood oxygenation, facilitate ventilation, reduce respiratory effort, and prevent intubation and complications associated with invasive ventilation. In 2012, a pilot study was published on a small group of 40 patients with moderate hypoxemia ($PaO_2/FiO_2$ in the 200–300 mm Hg range) who were randomized to NIV or high-flow oxygen therapy via a Venturi mask. A significant reduction in the number of intubations was found (1 patient in the NIV group and 7 patients in the oxygen therapy group, $p = 0.04$) as well as a positive trend towards lower mortality [51]. Unfortunately, this promising study was not repeated in a larger group of patients. Individual observational studies conducted in specialized intensive care centers also pointed to the possibility of beneficial effects of NIV in selected patients. However, the percentage of patients with NIV failure reached 50% in the case of pneumonia and ARDS [52, 53]. The reason for the frequent failure of NIV in the treatment of ARF can be explained by several factors:

1. Difficulty with controlling unintentional leaks;
2. The need to take breaks in conducting NIV due to individual variability in tolerance;
3. The possibility of stomach distension, which can significantly impair ventilation;

4. Difficulty in providing protective ventilation (small tidal volumes of approx. 6 mL/kg of predicted body weight) [54], especially in patients with a higher respiratory drive generating high transpulmonary pressures leading to ventilator-induced lung injury (VILI);
5. The inability to deeply sedate the patient in case of significant patient-ventilator asynchrony;
6. Difficulty in providing NIV in the prone position, which is beneficial in improving oxygenation in patients with ARDS [55], although some attempts have been made [47];
7. An inability to paralyze the patient's muscles, which would be beneficial in not only facilitating protective ventilation, but also improving the redistribution of blood from skeletal muscles to internal organs [56].

The main concern with regards to the treatment of patients with ARF with NIV is the potential delay of intubation and invasive ventilation. NIV failure is a predictive factor of higher mortality and complications associated with invasive ventilation. Risk factors for NIV failure include [53]:

1. Severe state of the patient, expressed by a high SAPS II score (Simplified Acute Physiology Score II) > 35 points;
2. > 40 years old;
3. Severe ARDS, $PaO_2/FiO_2$ < 100 mm Hg;
4. No improvement during the first hour of NIV, expressed as an oxygenation index of < 146 mm Hg after 1 hour.

NIV was used during the SARS epidemic in 2002 and during the swine flu virus epidemic in 2009. In the first case, the failure rate was about 30% [57], while in the second, it was highly variable and ranged from 13 to 77% [58]. Due to the lack of controlled studies about whether or not the use of NIV reduces the risk of intubation and death due to ARF in the course of viral pneumonia, the European Respiratory Society issued guidelines in 2017 in which they abstained from taking a position on the appropriateness of using NIV in such situations [59]. The use of BPAP should be considered in patients who cannot tolerate the administration of CPAP due to discomfort on expiration. The amount of pressure support should not markedly increase the tidal volume so as not to intensify the potential damaging effect on the lungs. It is believed that an inspiratory pressure 4–10 $cmH_2O$ higher than the expiratory pressure should effectively compensate for the effect of expiratory resistance while not generating large pressure differences during the breathing cycle. In summary, NIV can be conducted in the case of ARF when it presents with a mild or moderate hypoxemia, preferably in a center with experience in conducting this form of ventilatory support. This center should also be able to ensure constant monitoring of the patient with urgent access to intubation and invasive ventilation

### Treatment of an acute-on-chronic respiratory failure

In the case of a patient with COVID-19 also suffering from an acute exacerbation of chronic respiratory failure associated with hypercapnia (i.e. an exacerbation of COPD), the indications for the use of NIV are the same as for an acute exacerbation of COPD caused by any other different etiology. In such a clinical situation, the benefits of non-invasive ventilatory support are well documented and proven to reduce the risk of intubation, death, and complications associated with invasive ventilation [50]. Respiratory acidosis (pH < 7.35) is an indication for starting NIV. However, patients with chronic respiratory failure and COVID-19 may develop more severe hypoxemia, which could significantly reduce the efficacy of NIV.

## Monitoring of patients in non-ICU setting

The monitoring of every patient with COVID-19 is necessary for their proper management due to the potential risk of acute respiratory failure. In 2017 the British authors created the 'National Early Warning Score 2' (NEWS2) which can be helpful in monitoring patients at risk of respiratory failure [60]. It is simple to fill out and can be completed by lower qualified medical personnel (i.e. medical or nursing student). NEWS2 consists of information about vital signs, state of consciousness, and facts about their use of oxygen therapy. Each measurement value is converted into points, the sum of which indicates the type of intervention to be undertaken. The greater the sum of points, the more severe the patient's condition and the more frequent subsequent assessments that a patient requires.

In patients with severe respiratory failure requiring oxygen therapy with a high $FiO_2$ > 0.4, or treated with HFNOT or NIV, continuous monitoring of vital signs, especially $SpO_2$ and respiratory rate, should be required. This is because the patient's potential sudden deterioration will be an indication for intensified treatment (intubation and invasive ventilation), as long as there is no Do Not Resuscitate (DNR) order.

In 2016, Roca *et al*. created an index with the acronym ROX to predict the success of HFNOT in patients with acute respiratory failure due to pneumonia [61]. The ROX index combines three common measurements: $FiO_2$, $SpO_2$, and respiratory rate.

It is calculated according to the following formula:

$$ROX = \frac{SpO_2/FiO_2}{\text{breaths/min}}$$

For example, in a patient with a respiratory rate of 30/min and $SpO_2$ of 90%, with $FiO_2$ set at 0.50, the ROX index is 1.5. This index is based on the assessment of two elements in the functioning of the respiratory system which, on one hand, are simple to measure, and on the other, reflect its functioning very well. These are respiratory rate, which reflects respiratory effort and the $SpO_2/FiO_2$ ratio, which highlights the degree of impairment of gas exchange. Higher oxygen concentrations necessary to maintain an adequate $SpO_2$ and a higher respiratory rate are evidence of a greater impairment of respiratory function and thus a higher risk of failure of HFNOT. Among the components of this index, $SpO_2/FiO_2$ had a greater value than the respiratory rate. These observations confirm the importance of using the right amount of $FiO_2$ in increasing the chance of success with HFNOT [62]. The prognostic value of the ROX index was verified during a multicentre, prospective study involving 191 patients with pneumonia [63]. This study showed that ROX ≥ 4.88 after 2, 6, or 12 hours of HFNOT indicated success. While values ≤ 2.85 after 2 hours, ≤ 3.47 after 6 hours, and ≤ 3.85 after 12 hours of using HFNOT testified to its inefficacy. It should be remembered that the reliability of the ROX index has not yet been assessed in patients with COVID-19. In 2019, the monitoring and management algorithm for using HFNOT for acute hypoxemic respiratory failure was updated [31] and took into account the ROX index and the latest reports on prognostic index values [33].

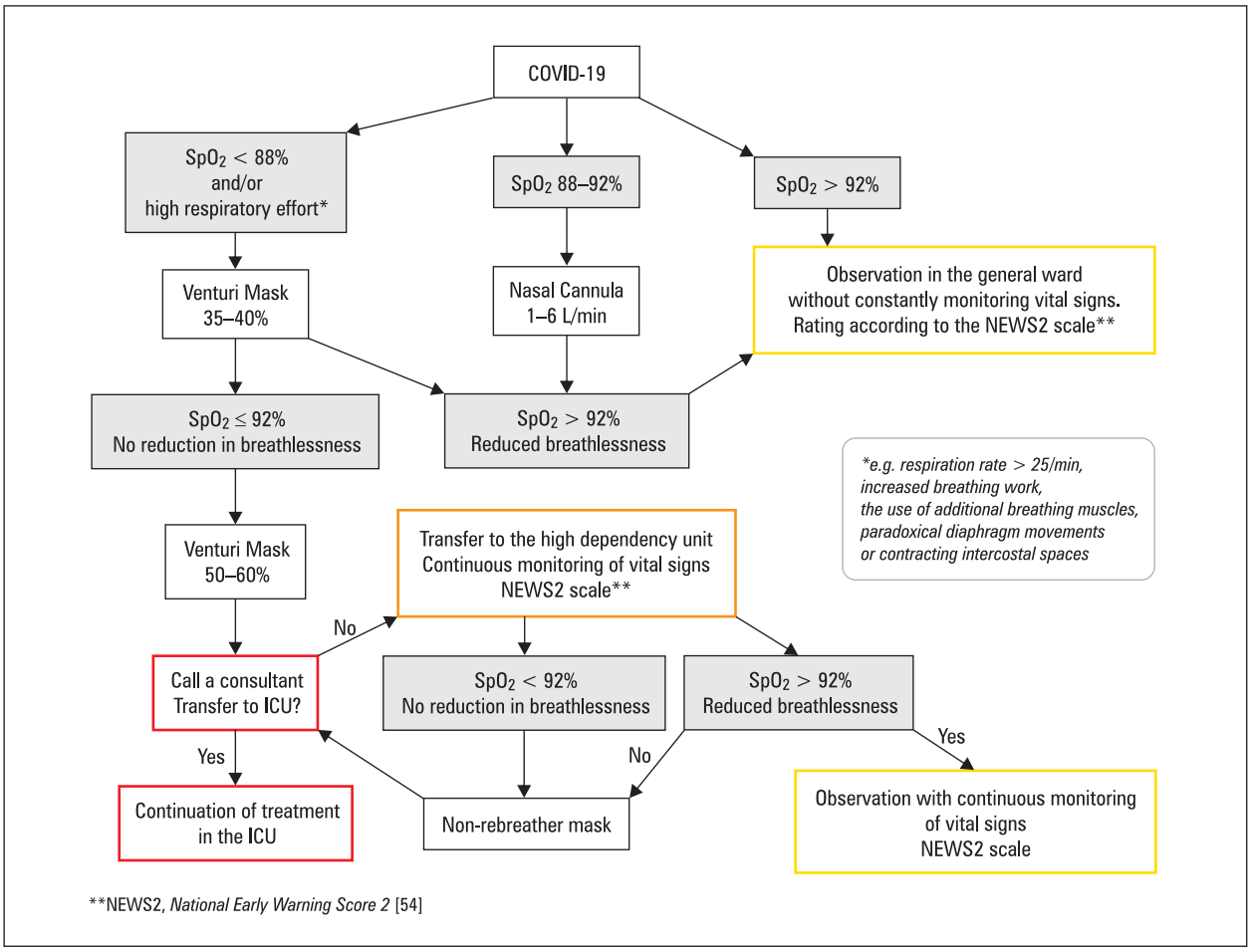


**Figure 18.** Algorithms for the treatment of respiratory failure in COVID-19 in general ward with the use of conventional of oxygen therapy

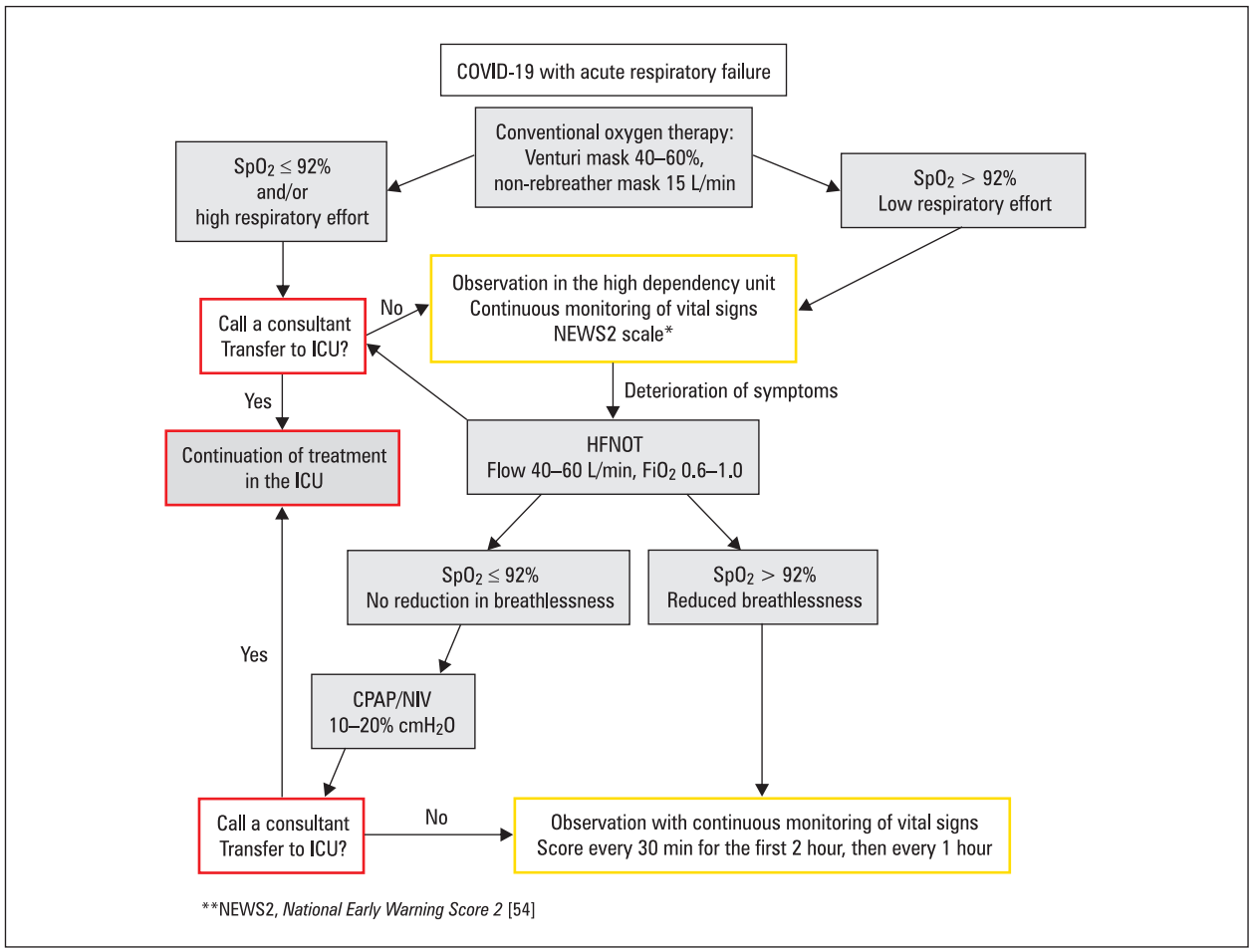


**Figure 19**. Algorithms for the treatment of respiratory failure in COVID-19 with the use of conventional and advanced technics of oxygen therapy (HFNOT, CPAP, NIV)

Algorithms for the treatment of respiratory failure in COVID-19 outside of the ICU are shown in Figures 18 and 19.

## Invasive ventilation

In situations where the above-mentioned methods of treatment of respiratory failure prove to be ineffective, indications for invasive ventilation should be established after anesthesia consultation. These indications include:

1. From a clinical point of view: significant respiratory effort with signs of inspiratory muscle fatigue and failure of other organs and systems — cardiologic, hemodynamic, and disorders of consciousness;
2. From a pathophysiological point of view: severe hypoxemia and/or severe hypercapnia with or without respiratory acidosis that is not improving or is worsening despite intensive treatment.

In the course of the SARS-CoV-2 infection, ARDS may develop. It is not a primary lung disease but a type of extensive inflammatory process in the lungs stemming from various etiologies. ARDS in the course of COVID-19 often develops rapidly and unpredictably. From a practical point of view, it is important to know the criteria for the diagnosis and classification of ARDS, as well as the general principles of ARDS treatment associated with the use of invasive ventilation.

In 2012, an international group of experts established a new definition called the "Berlin definition" [64]. This re-organized definition was made in order to facilitate a more accurate diagnosis of ARDS and to allow for a better adaptation of therapeutic management linked to the severity of this syndrome, both in clinical trials and in everyday practice. It was agreed that ARDS is a type of sudden injury due to inflammatory factors acting on the lungs, which leads

to increased pulmonary vascular permeability, and loss of lung parenchyma. Markers of this clinical syndrome are severe hypoxemia, bilateral parenchymal lung lesions corresponding to non-cardiogenic pulmonary edema (in standard chest radiography or computed tomography), and pathophysiological disorders such as right-to-left shunt, increased dead space, and decreased lung compliance. There are four criteria necessary for the diagnosis of ARDS:

1. Time criteria: the appearance of new or worsening existing respiratory symptoms within 1 week;
2. Radiological criteria: bilateral parenchymal infiltrates that are not caused by exudate, atelectasis, or tumor;
3. Causal criteria: respiratory failure not due to heart failure or fluid overload; an objective assessment (i.e. echocardiography) is required in order to exclude hydrostatic edema if ARDS risk factors are not present;
4. Gasometric criteria: forms the basis for classifying severity of ARDS.

The basis for this classification is based on the oxygenation index (i.e. the ratio of $PaO_2$ to $FiO_2$). In this regard, there is:

— mild ARDS: 200 mm Hg < $PaO_2/FiO_2$ ≤ 300 mm Hg with PEEP/CPAP ≥ 5 $cmH_2O$;
— moderate ARDS: 100 mm Hg < $PaO_2/FiO_2$ ≤ 200 mm Hg with PEEP ≥ 5 $cmH_2O$;
— severe ARDS: $PaO_2/FiO_2$ ≤ 100 mm Hg with PEEP ≥ 5 $cmH_2O$.

The three above-mentioned categories of mild, moderate, and severe ARDS were created to ensure risk stratification and improve the choice of treatment method and setting. At the same time, the widely used term "acute lung injury" (ALI) has been removed from the definition of ARDS. In the new classification, each ARDS category (mild, moderate, severe) is defined by mutually exclusive ranges of $PaO_2/FiO_2$ values. The creation of a mild category of ARDS formalizes what was previously seen as a less severe form of the syndrome. Finally, by introducing the term mild ARDS, the severity of the disease (27% mortality) and response to protective lung ventilation were recognized.

Over the past 20 years, many clinical studies have been conducted with the goal of developing an optimal treatment for ARDS [65]. Most of them were performed by a group of researchers associated with the ARDS-Network. The ARDS-Network protocol, referred to as the Lung Protective Strategy, should be implemented into standardized practice for the treatment of ARDS in intensive care units. Of the several test modes of rescue ventilation in ARDS [high PEEP ventilation, recruitment maneuvers, prone position, inverse ratio ventilation (IRV), airway pressure release ventilation (APRV), and high frequency oscillation (HFO)], only prone position proved to be a method that improved ventilation with scientifically documented significance. The use of neuromuscular blockade has also been shown to be an important aspect of improving the effectiveness of ventilation in severe ARDS, but remains controversial [56]. From the evaluated rescue therapies in ARDS (surfactant, NO inhalation, extracorporeal $CO_2$ removal, and extracorporeal oxygenation), only extracorporeal membrane oxygenation (ECMO) proved to be therapeutically valuable in the treatment of ARDS, although the effectiveness of most these techniques were not evaluated in controlled studies in acute respiratory failure in COVID-19.

## Extracorporeal gas exchange support

Extracorporeal gas exchange support is the most advanced alternative method to mechanical ventilation in terms of respiratory support. Its task is to replace gas exchange in the lungs while they recover. It consists of two techniques: extracorporeal membrane oxygenation (ECMO) and extracorporeal carbon dioxide removal ($ECCO_2R$). The $ECCO_2R$ device is a variant of ECMO characterized by low blood flow and reduced blood oxygenation with a less invasive technique that uses much smaller vascular cannulas. Extracorporeal oxygenation of blood involves the use of a modified extracorporeal circulation apparatus, which is intended for long-term use. There are two types of ECMO:

1. Veno-arterial ECMO: replaces the work of the heart and lungs and is used in the most severe circulatory-respiratory distress syndromes because, apart from blood oxygenation, it generates mechanical circulatory support;
2. Veno-venous ECMO: supports the work of the lungs and is used in respiratory failure.

Currently, the role of this method in supporting respiration was established after the publication of the results of the CESAR study in 2009 and EOLIA study in 2017, which state that ECMO can be considered an effective rescue method for patients who did not benefit from the use of optimal invasive ventilation (prone position, neuromuscular blockade, and use of high PEEP).

In Poland, the detailed recommendations and guidelines of the ECMO Venous Therapy Team were developed in the form of a protocol

and published in its original form in 2009 and then updated in 2016 [66]. These indications apply in full to the use of ECMO in the SARS-CoV-2 pandemic. In practice, a pneumonologist should generally consider the possibility of using veno-venous ECMO in two clinical situations:

1. A severe form of acute respiratory failure when gas exchange cannot be provided by conventional mechanical ventilation and respiratory failure is potentially reversible;
2. Theoretically, as a bridge for lung transplantation patients with end-stage respiratory failure [67].

According to Polish guidelines, the most important contraindication to ECMO therapy is the irreversibility of the disease. In addition, other contraindications for this method of treatment include: severe systemic disease, immunosuppression, intracranial hemorrhage, contraindications to anticoagulation therapy, invasive ventilation for over 7–10 days, lack of treatment with a respirator according to the Lung Protective Strategy, lack of consent of the patient, and over 65 years of age. ECMO therapy should be discontinued when there is extensive ischemia of the brain, massive intracranial bleeding, a diagnosis of another incurable disease, and in the absence of improvement of respiratory function despite therapy [66].

## Summary

The COVID-19 disease is mild in approx. 80% of cases, but other patients require hospitalization and a large proportion of them develop viral pneumonia. The consequence of this is acute hypoxic respiratory failure. In the SARS-CoV-2 pandemic era, knowledge of how to treat respiratory failure is important. All physicians should have this knowledge because treating patients with COVID-19 may be the responsibility of not only specialists in respiratory or intensive care medicine, but also the responsibility of doctors who do not deal with the treatment of respiratory failure in their daily practice. Therefore, the main target audience of this review are not so much pulmonologists who have extensive experience in applying the techniques discussed here, but rather doctors of other specialties, who in the age of pandemics must master new skills.

In the absence of specific and causal treatments for COVID-19, the primary therapeutic task is symptomatic management, which consists of ensuring adequate oxygenation of the blood. The optimal $SpO_2$ value that should be maintained is considered to be between 92–96%. The first step in the treatment of hypoxic respiratory failure is oxygen therapy. It can be guided by the following methods: nasal cannula, simple oxygen mask, Venturi mask, or a non-rebreather mask. Choosing the right technique depends primarily on the effectiveness of obtaining adequate oxygenation, and secondly, on the patient's tolerance of the treatment. If treatment with oxygen therapy is ineffective, high-flow nasal oxygen therapy can be used. This is a relatively new treatment method, which due to its simple technique and high efficiency, is increasingly used in clinical practice. It is more effective than conventional oxygen therapy because it improves $SpO_2$ and reduces respiratory effort. Its advantage over passive oxygen therapy is that, apart from the supply of a gas mixture with a high (up to 100%) oxygen content, it also generates a low positive airway pressure. Thanks to this, it is considered a method that is in-between passive and active oxygen therapy. Active oxygen therapy refers to administration of inspiratory gases with positive airway pressure. This results in improved gas exchange in the alveolar recruitment mechanism. Oxygen therapy methods using positive airway pressure include CPAP and non-invasive mechanical ventilation (BiPAP). Considering the risk of personnel being infected by aerosol droplets from the patient's exhaled air, the best interface for using CPAP/BiPAP is a helmet or face mask. Since these interfaces are unvented, they do not allow the exhaled air to spread directly into the room without passing through the filter.

Patients with mild respiratory failure can be hospitalized without constant monitoring. The NEWS2 scale is recommended to assess their condition. In the event of moderate or severe hypoxemia, vital signs, including primarily $SpO_2$ and respiratory rate, must be monitored continuously. These patients should be placed in a high dependency unit. The main purpose of monitoring is to control the effectiveness of treatment by maintaining adequate $SpO_2$, reducing shortness of breath and breathing effort. In the absence of improvement during the first two hours of treatment, consideration should be given to admit the patient to the ICU because of the high risk of intubation and invasive mechanical ventilation. Delaying this form of treatment can be associated with a higher mortality. In selected patients who do not improve despite the properly conducted invasive ventilation, the use of extracorporeal membrane oxygenation may be considered.

The authors of this article intended to present the most current knowledge about the epidemi-

ology and pathophysiology of respiratory failure in the course of COVID-19, as well as the methods of its treatment. Given the dynamics of the development of a pandemic, this is not an easy task as new scientific data is reported almost every day. However, we believe that the knowledge contained in this review will help doctors in the care of patients with respiratory failure due to COVID-19.

## Conflict of interest

None declared.

## References:


1. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. Available at: www.who.int/csr/sars/country/table2004_04_21/en/. [Last accessed at: 30.04.2020].
2. Mackay IM, Arden KE. MERS coronavirus: diagnostics, epidemiology and transmission. Virol J. 2015; 12: 222, doi: 10.1186/s12985-015-0439-5, indexed in Pubmed: 26695637.
3. Plipat T, Buathong R, Wacharapluesadee S, et al. Imported case of Middle East respiratory syndrome coronavirus (MERS-CoV) infection from Oman to Thailand, June 2015. Euro Surveill. 2017; 22(33), doi: 10.2807/1560-7917.ES.2017.22.33.30598, indexed in Pubmed: 28840828.
4. Zhang H, Penninger JM, Li Y, et al. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med. 2020; 46(4): 586–590, doi: 10.1007/s00134-020-05985-9, indexed in Pubmed: 32125455.
5. Worldmeters. Coronavirus Cases. Available at: www.worldometers. [Last accessed at: 30.04.2020].. info/coronavirus/ 30.; 04: 2020.
6. Guan WJ, Ni ZY, Hu Yu, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020; 382(18): 1708–1720, doi: 10.1056/NEJMoa2002032, indexed in Pubmed: 32109013.
7. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395(10229): 1054–1062, doi: 10.1016/S0140-6736(20)30566-3, indexed in Pubmed: 32171076.
8. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020 [Epub ahead of print], doi: 10.1001/jamainternmed.2020.0994, indexed in Pubmed: 32167524.
9. Omer SB, Malani P, Del Rio C. The COVID-19 pandemic in the US: A clinical update. JAMA. 2020 [Epub ahead of print], doi: 10.1001/jama.2020.5788, indexed in Pubmed: 32250388.
10. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to icus of the Lombardy Region, Italy. JAMA. 2020 [Epub ahead of print], doi: 10.1001/jama.2020.5394, indexed in Pubmed: 32250385.
11. Lippi G, Henry BM. Chronic obstructive pulmonary disease is associated with severe coronavirus disease 2019 (COVID-19). Respir Med. 2020; 167: 105941, doi: 10.1016/j.rmed.2020.105941, indexed in Pubmed: 32421537.
12. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA. 2020 [Epub ahead of print], doi: 10.1001/jama.2020.4326, indexed in Pubmed: 32191259.
13. Wang D, Hu Bo, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020 [Epub ahead of print], doi: 10.1001/jama.2020.1585, indexed in Pubmed: 32031570.
14. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020; 8(5): 475–481, doi: 10.1016/S2213-2600(20)30079-5, indexed in Pubmed: 32105632.
15. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. 2020; 46(6): 1099–1102, doi: 10.1007/s00134-020-06033-2, indexed in Pubmed: 32291463.
16. Poissy J, Goutay J, Caplan M, et al. Pulmonary embolism in COVID-19 patients: awareness of an increased prevalence. Circulation. 2020 [Epub ahead of print], doi: 10.1161/CIRCULATIONAHA.120.047430, indexed in Pubmed: 32330083.
17. O'Driscoll BR, Howard LS, Earis J, et al. BTS guideline for oxygen use in adults in healthcare and emergency settings. Thorax. 2017; 72(Suppl 1): ii1–ii90, doi: 10.1136/thoraxjnl-2016-209729, indexed in Pubmed: 28507176.
18. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: Interim guidance V 1. 2020.
19. Siemieniuk RAC, Chu DK, Kim LHY, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. BMJ. 2018; 363: k4169, doi: 10.1136/bmj.k4169, indexed in Pubmed: 30355567.
20. Alhazzani W, Møller MH, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Intensive Care Med. 2020; 46(5): 854–887, doi: 10.1007/s00134-020-06022-5, indexed in Pubmed: 32222812.
21. Hui DS, Hall SD, Chan MTV, et al. Exhaled air dispersion during oxygen delivery via a simple oxygen mask. Chest. 2007; 132(2): 540–546, doi: 10.1378/chest.07-0636, indexed in Pubmed: 17573505.
22. Hui DSC, Chan MTV, Chow B. Aerosol dispersion during various respiratory therapies: a risk assessment model of nosocomial infection to health care workers. Hong Kong Med J. 2014; 20 Suppl 4: 9–13, indexed in Pubmed: 25224111.
23. Dysart K, Miller TL, Wolfson MR, et al. Research in high flow therapy: mechanisms of action. Respir Med. 2009; 103(10): 1400–1405, doi: 10.1016/j.rmed.2009.04.007, indexed in Pubmed: 19467849.
24. Nishimura M. High-Flow nasal cannula oxygen therapy in adults: physiological benefits, indication, clinical benefits, and adverse effects. Respir Care. 2016; 61(4): 529–541, doi: 10.4187/respcare.04577, indexed in Pubmed: 27016353.
25. Sun Q, Qiu H, Huang M, et al. Lower mortality of COVID-19 by early recognition and intervention: experience from Jiangsu Province. Ann Intensive Care. 2020; 10(1): 33, doi: 10.1186/s13613-020-00650-2, indexed in Pubmed: 32189136.
26. Rello J, Pérez M, Roca O, et al. CRIPS investigators. High-flow nasal therapy in adults with severe acute respiratory infection: a cohort study in patients with 2009 influenza A/H1N1v. J Crit Care. 2012; 27(5): 434–439, doi: 10.1016/j.jcrc.2012.04.006, indexed in Pubmed: 22762937.
27. Coudroy R, Frat JP, Ehrmann S, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015; 372(23): 2185–2196, doi: 10.1056/NEJMoa1503326, indexed in Pubmed: 25981908.
28. Rochwerg B, Granton D, Wang DX, et al. High flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: a systematic review and meta-analysis. Intensive Care Med. 2019; 45(5): 563–572, doi: 10.1007/s00134-019-05590-5, indexed in Pubmed: 30888444.
29. Ni YN, Luo J, Yu He, et al. The effect of high-flow nasal cannula in reducing the mortality and the rate of endotracheal intubation when used before mechanical ventilation compared with conventional oxygen therapy and noninvasive positive pressure ventilation. A systematic review and meta-analysis. Am J Emerg Med. 2018; 36(2): 226–233, doi: 10.1016/j.ajem.2017.07.083, indexed in Pubmed: 28780231.
30. Spoletini G, Alotaibi M, Blasi F, et al. Heated humidified high-flow nasal oxygen in adults: mechanisms of action and clinical implications. Chest. 2015; 148(1): 253–261, doi: 10.1378/chest.14-2871, indexed in Pubmed: 25742321.

31. Ischaki E, Pantazopoulos I, Zakynthinos S. Nasal high flow therapy: a novel treatment rather than a more expensive oxygen device. Eur Respir Rev. 2017; 26(145), doi: 10.1183/16000617.0028-2017, indexed in Pubmed: 28794144.
32. Miguel-Montanes R, Hajage D, Messika J, et al. Use of high-flow nasal cannula oxygen therapy to prevent desaturation during tracheal intubation of intensive care patients with mild-to-moderate hypoxemia. Crit Care Med. 2015; 43(3): 574–583, doi: 10.1097/CCM.0000000000000743, indexed in Pubmed: 25479117.
33. Ischaki E, Pantazopoulos I. "Blow with the high flow" an updated algorithm. Journal of Emergency and Critical Care Medicine. 2019; 3: 61–61, doi: 10.21037/jeccm.2019.10.03.
34. Hui DS, Chow BK, Lo T, et al. Exhaled air dispersion during high-flow nasal cannula therapy CPAP different masks. Eur Respir J. 2019; 53(4), doi: 10.1183/13993003.02339-2018, indexed in Pubmed: 30705129.
35. Raboud J, Shigayeva A, McGeer A, et al. Risk factors for SARS transmission from patients requiring intubation: a multicentre investigation in Toronto, Canada. PLoS One. 2010; 5(5): e10717, doi: 10.1371/journal.pone.0010717, indexed in Pubmed: 20502660.
36. Kluge S, Janssens U, Welte T, et al. German recommendations for critically ill patients with COVID19. Med Klin Intensivmed Notfmed. 2020 [Epub ahead of print], doi: 10.1007/s00063-020-00689-w, indexed in Pubmed: 32291505.
37. Patil SP, Ayappa IA, Caples SM, et al. Treatment of adult obstructive sleep apnea with positive airway pressure: an american academy of sleep medicine clinical practice guideline. J Clin Sleep Med. 2019; 15(2): 335–343, doi: 10.5664/jcsm.7640, indexed in Pubmed: 30736887.
38. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med. 2004; 351(4): 327–336, doi: 10.1056/NEJMoa032193, indexed in Pubmed: 15269312.
39. Lau ACW, Yam LYC, So LKY. Management of critically ill patients with severe acute respiratory syndrome (SARS). Int J Med Sci. 2004; 1(1): 1–10, doi: 10.7150/ijms.1.1, indexed in Pubmed: 15912185.
40. Hick J, Hanfling D, Wynia M, et al. Duty to plan: health care, crisis standards of care, and novel coronavirus SARS-CoV-2. NAM Perspectives. 2020, doi: 10.31478/202003b.
41. McCann UG, Schiller HJ, Carney DE, et al. Visual validation of the mechanical stabilizing effects of positive end-expiratory pressure at the alveolar level. J Surg Res. 2001; 99(2): 335–342, doi: 10.1006/jsre.2001.6179, indexed in Pubmed: 11469907.
42. National Institute for Health and Care Excellence. COVID-19 rapid guideline: critical care in adults. NICE guideline. Available at: https://www.nice.org.uk/guidance/ng159. [Last accessed at: 30.04.2020].
43. Hui DS, Chow BK, Lo T, et al. Exhaled air dispersion during noninvasive ventilation via helmets and a total facemask. Chest. 2015; 147(5): 1336–1343, doi: 10.1378/chest.14-1934, indexed in Pubmed: 25392954.
44. Wong DT, Tam AD, Van Zundert TC. The usage of the Boussignac continuous positive airway pressure system in acute respiratory failure. Minerva Anestesiol. 2013; 79(5): 564–570, indexed in Pubmed: 23419338.
45. Volsko TA. Devices used for CPAP delivery. Respir Care. 2019; 64(6): 723–734, doi: 10.4187/respcare.06625, indexed in Pubmed: 31110040.
46. Guidance regarding coronavirus (COVID-19) and obstructive sleep apnoea (OSA): for people who routinely use continuous positive airway pressure (CPAP), their families and health care workers. Available at: www.brit-thoracic.org.uk/media/455098/osa-alliance-cpap-covid-19-advice-20-3-20-v10.pdf. [Last accessed at: 30.04.2020].
47. Ding L, Wang Li, Ma W, et al. Efficacy and safety of early prone positioning combined with HFNC or NIV in moderate to severe ARDS: a multi-center prospective cohort study. Crit Care. 2020; 24(1): 28, doi: 10.1186/s13054-020-2738-5, indexed in Pubmed: 32000806.
48. Elharrar X, Trigui Y, Dols AM, et al. Use of prone positioning in nonintubated patients with COVID-19 and hypoxemic acute respiratory failure. JAMA. 2020 [Epub ahead of print], doi: 10.1001/jama.2020.8255, indexed in Pubmed: 32412581.
49. Sartini C, Tresoldi M, Scarpellini P, et al. Respiratory parameters in patients with COVID-19 after using noninvasive ventilation in the prone position outside the intensive care unit. JAMA. 2020 [Epub ahead of print], doi: 10.1001/jama.2020.7861, indexed in Pubmed: 32412606.
50. Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017; 50(2), doi: 10.1183/13993003.02426-2016, indexed in Pubmed: 28860265.
51. Zhan Q, Sun B, Liang L, et al. Early use of noninvasive positive pressure ventilation for acute lung injury: a multicenter randomized controlled trial. Crit Care Med. 2012; 40(2): 455–460, doi: 10.1097/CCM.0b013e318232d75e, indexed in Pubmed: 22020236.
52. Antonelli M, Conti G, Esquinas A, et al. A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. Crit Care Med. 2007; 35(1): 18–25, doi: 10.1097/01.M.0000251821.44259.F3, indexed in Pubmed: 17133177.
53. Antonelli M, Conti G, Moro ML, et al. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. Intensive Care Med. 2001; 27(11): 1718–1728, doi: 10.1007/s00134-001-1114-4, indexed in Pubmed: 11810114.
54. Chen J, Lin J, Luo H, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000; 342(18): 1301–1308, doi: 10.1056/NEJM200005043421801, indexed in Pubmed: 10793162.
55. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013; 368(23): 2159–2168, doi: 10.1056/NEJMoa1214103, indexed in Pubmed: 23688302.
56. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med. 2010; 363(12): 1107–1116, doi: 10.1056/NEJMoa1005372, indexed in Pubmed: 20843245.
57. Cheung TMT, Yam LYC, So LKY, et al. Effectiveness of noninvasive positive pressure ventilation in the treatment of acute respiratory failure in severe acute respiratory syndrome. Chest. 2004; 126(3): 845–850, doi: 10.1378/chest.126.3.845, indexed in Pubmed: 15364765.
58. Estenssoro E, Ríos FG, Apezteguía C, et al. Pandemic 2009 influenza A in Argentina: a study of 337 patients on mechanical ventilation. Am J Respir Crit Care Med. 2010; 182(1): 41–48, doi: 10.1164/201001-0037OC, indexed in Pubmed: 20203241.
59. Raghu G, Rochwerg B, Zhang Y, et al. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. Am J Respir Crit Care Med. 2015; 192(2): e3–19, doi: 10.1164/rccm.201506-1063ST, indexed in Pubmed: 26177183.
60. Royal College of Physicians. National Early Warning Score (NEWS): standardising the assessment of acute-illness severity in the NHS. Report of a working party. London: RCP, 2017. Available at: www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2 [Last accessed: 30.05.2020].
61. Roca O, Messika J, Caralt B, et al. Predicting success of high-flow nasal cannula in pneumonia patients with hypoxemic respiratory failure: The utility of the ROX index. J Crit Care. 2016; 35: 200–205, doi: 10.1016/j.jcrc.2016.05.022, indexed in Pubmed: 27481760.
62. Tatkov S. Nasal high-flow therapy: role of fi in the ROX index. Am J Respir Crit Care Med. 2019; 200(1): 115–116, doi: 10.1164/rccm.201902-0376LE, indexed in Pubmed: 30896967.
63. Roca O, Caralt B, Messika J, et al. An index combining respiratory rate and oxygenation to predict outcome of nasal high-flow therapy. Am J Respir Crit Care Med. 2019; 199(11): 1368–1376, doi: 10.1164/rccm.201803-0589OC, indexed in Pubmed: 30576221.
64. Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med. 2012; 38(10): 1573–1582, doi: 10.1007/s00134-012-2682-1, indexed in Pubmed: 22926653.
65. Griffiths MJD, McAuley DF, Perkins GD, et al. Guidelines on

the management of acute respiratory distress syndrome. BMJ Open Respir Res. 2019; 6(1): e000420, doi: 10.1136/bmjresp-2019-000420, indexed in Pubmed: 31258917.
66. Lango R, Szkulmowski Z, Maciejewski D, et al. Revised protocol of extracorporeal membrane oxygenation (ECMO) therapy in severe ARDS. Recommendations of the Veno-venous ECMO Expert Panel appointed in February 2016 by the national consultant on anesthesiology and intensive care. Anaesthesiol Intensive Ther. 2017; 49(2): 88–99, doi: 10.5603/AIT.a2017.0028, indexed in Pubmed: 28643320.
67. Chen JY, Qiao K, Liu F, et al. Lung transplantation as therapeutic option in acute respiratory distress syndrome for coronavirus disease 2019-related pulmonary fibrosis. Chin Med J (Engl). 2020; 133(12): 1390–1396, doi: 10.1097/CM9.0000000000000839, indexed in Pubmed: 32251003.
68. Boussignac CPAP System. Available at: www.yumpu.com/en/document/read/29383460/cpap-system-lma-north-america. [Last accessed: 31.05.2020].